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CLINICAL ASPECTS OF DRUG-INDUCED DISEASES OF THE LIVER

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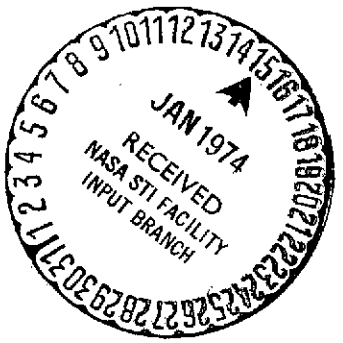

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CLINICAL ASPECTS OF DRUG-INDUCED DISEASES OF THE LIVER

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The preceding talks have reported on the processes available /343* to the body for transporting administered medications into the blood, rearranging and degrading them in the liver to detoxify them, and eliminating them. We have also heard how the mutual influences of medications can act on the human organism, and how small the step is from the best adaptation to toxic or injurious action. In addition, we have learned which morphological changes should be related to adaptation processes and which to injury, and that here, too, the transition from one to the other can be very difficult to determine.

For a clinician, it is important that he draws, and can draw, his own lessons from biochemical and morphological discoveries. For each of the steps indicated there are clinical correspondences which we should define as perturbations or as disease units. In this respect, the words of the clinician Ludolf v. Krehl occur spontaneously to us. He defined "disease as life at the limit of adaptation". If we follow the individual steps, then we have the following possibilities for disturbed function, which are among others stated as definite guiding symptoms (Table 1).

* Numbers in the margin indicate pagination in the original foreign text.

Table 1. GUIDING SYMPTOMS IN DRUG-INDUCED DAMAGE

1. Hyperbilirubinemia — icterus
2. Hepatomegaly with and without jaundice
3. Allergic reaction (skin and blood)
4. Cholestasis (with or without 1, 2, 3)
5. Hepatitis (with or without 1, 2, 3, 4)
6. Hemorrhagic diathesis

Hyperbilirubinemia from medication can have different causes (Table 2): / 344

Table 2. HYPERBILIRUBINEMIA WITHOUT LIVER INJURY, FROM:

1. Hemolysis (example: phenacetin)
2. Altered protein binding (example: sulfonamides)
3. Competition at the x- or y-proteins of the liver cells (example: rifamycin)
4. Enzyme inhibition (example: novobiocin)

1) Drugs can change the bilirubin metabolism so that the bilirubin load is increased so much through hemolysis that the liver cells are overloaded by the increased stress. In many cases the hemolytic reaction goes along with damage to the liver cell function. Such reactions are observed, for instance, after para-aminosalicylic acid and after phenacetin, when the drug-erythrocyte complex acts as an antigen. With enzyme defects in the erythrocytes, the same or other drugs can lead to hemolysis and jaundice. It is important that with significant enzyme defect these drugs also cause jaundice in the newborn if the mother passes the drug on to the infant through the milk. The

toxic action of synthetic Vitamin K is partially due to increased hemolysis.

2) Protein binding: Other drugs displaced the unconjugated bilirubin from its binding to protein. The unbound bilirubin passes more easily through the blood-fluid compartment and leads to nuclear icterus in the infant even at relatively low bilirubin values. Displacements of this type are observed after salicylates and sulfonamides.

3) Some drugs, such as flavaspinic acid from the fern, rifamycin and novobiocin have the property of competing with the unconjugated bilirubin in the liver cell. Two carrier proteins in the liver cell, the x- and y-proteins, transport the unconjugated bilirubin through the cell. Jaundice occurs if one of the carriers is occupied by the drug.

4. Enzyme inhibition or induction: The antibiotic novobiocin inhibits uridine diphospho-glucuronyl transferase, thus leading to a rise in indirect bilirubin. This can again lead to nuclear icterus in the newborn.

On the other hand, it is possible to influence indirect hyperbilirubinemia by inducing the enzyme glucuronyl transferase with phenobarbital. This effect is used therapeutically, with women receiving 30-120 mg phenobarbital 2 weeks before the expected delivery. The conjugated bilirubin is not, or very little, affected by phenobarbital.

Hepatomegaly / 345

Hepatomegaly can occur as the only clinical sign of a slow drug action with liver damage. Table 3 summarizes the most frequent causes of iatrogenic liver enlargement. This includes

simple enlargement, fatty liver, granuloma development, storage of foreign materials and peliosis. Only rarely does liver enlargement from the above-mentioned causes give rise to complaints.

Table 3. HEPATOMEGALY AS A DRUG EFFECT, CAUSED BY:

1. Simple enlargement without detectable morphologic change (example: phenobarbital, halothane, cortisone, etc.)
2. Fatty liver (example: tetracycline, cortisone)
3. Granuloma development (example: phenylbutazone, sulfonylurea)
4. Storage (example: thorotrast, polyvinylpyrrolidone)
5. Peliosis (example: anabolic steroids)

Cholestasis

This form of drug-induced liver damage is characterized in most cases by blockage of bile flow. The clinical characteristics are jaundice and itching, direct hyperbilirubinemia, bilirubinuria, elevation of the serum alkaline phosphatase and of cholesterol and, less distinctly, of the transaminases.

Following anabolic steroids such as norethandrolone it is possible to follow a dose-dependent transition from anicteric cholestasis to fully expressed jaundice. The anicteric form can be demonstrated by increased bromsulfalein retention. The contraceptive steroids are also in this group. In most cases these consist of a combination of a synthetic progestogen and an estrogen in a ratio of 10:1. Both components are among the C-17-α-alkyl-substituted 19-nor-steroids. The C-17 alkylation which this preparation has in common with the cholestasis-producing testosterone derivatives is responsible for the disturbance of the liver function. Table 4 summarizes the major

functional disturbances observed. In this case, pathologic bromsulfalein retention cannot be evaluated as a reliable sign of liver damage because it occurs through limitation of the liver cell maximum transport for conjugated bromsulfalein.

Table 4: DOSE-DEPENDENT CHOLESTASIS:

1. Anabolic and contraceptive steroids. Alkylation at C-17 appears linked to icterogenic properties, although this is not obligatory.
2. Effect is dose-dependent.
3. Brief icterus, itching, elevated transaminases, serum alkaline phosphatase and serum cholesterol.
4. Jaundice may be absent. Increased BSP retention. Dilated canaliculi, loss of the microvilli.

The disturbances listed above occur without jaundice in most / 346 cases. Some 0.01 - 0.1% of all women who take the "pill" develop jaundice. It is striking that the frequency of jaundice on taking the pill differs very much geographically. One certain frequency has been observed in Chile and Sweden, where one case of jaundice has been observed in every 4,000 women taking the pill. Probably our frequency corresponds to that in the USA, 1:10,000. The duration of the medication is from a few weeks to months. Women who have experienced pruritis or a so-called recurrent icterus of pregnancy in the last third of pregnancy react in the same way if they take an ovulation inhibitor. Women with functional hyperbilirubinemia can react in the same way. In these cases, administration of contraceptive hormones is contraindicated under some circumstances.

Cholestasis as a hypersensitivity reaction: A large number of medications can cause jaundice with cholestasis as an expression of a hypersensitivity reaction. These medications include phenothiazine and sulfonylurea derivatives. This disease picture was first observed following organic arsenic preparations. Table 5 summarizes the most important medications.

Table 5. CHOLESTASIS AND HYPERSENSITIVITY:

Frequency: 1 - 2%
Sulfonyl urea derivatives
Chlorpromazine and other phenothiazines
Organic arsenic compounds
Erythromycin estolate
Triacetyloleandomycin
Na-oxazillin
Chlordiazepoxide
Centrolobular cholestasis plus inflammation
Inflammation disappears after 6-12 weeks.

In sensitive persons, the reaction with fever, pain in the upper right abdomen and exanthema must raise the suspicion of iatrogenic damage, which can proceed with or without jaundice. Among the disease symptoms already mentioned and the biochemical findings, the blood changes must be stressed particularly. In some 50% of all cases one finds a distinct blood eosinophilia.

Different frequencies have been measured for the various drugs. It is illuminating that the undesired effects appear more distinctly for those drugs most often given. For instance, we must expect up to 1% jaundice with the chlorpromazine preparations. It is considerably less for the other drugs.

As this jaundice can occur as an obstructive syndrome with pain and fever, it is easily confused with jaundice from a mechanical cause. It is important to detect this by careful anamnesis and to protect the patient from unnecessary surgery. / 347 These patients tolerate operations poorly and the few observations with fatal outcome are almost exclusively due to stresses from the operation.

It has already been stated that jaundice almost always is mild and disappears quickly after the drug responsible for it is stopped. Only in a few exceptional cases are courses of up to several months duration observed, with the disease picture being the same as that of primary biliary cirrhosis. But complete cure can occur even after many months of jaundice. The few observations which report on a transition to primary biliary cirrhosis allow the explanation that here the drug has only incited the spontaneous development of this disease picture. One important differential feature is apparently the mitochondrial immunofluorescence test, which is almost always positive in primary biliary cirrhosis.

Drug damage with hepatitis-like course

A number of drugs can cause hepatocullular injury to the liver which is in no way different from virus hepatitis. The oldest of the drugs to be recognized as damaging to the liver was atophane, which was still notably present among the drugs used in Germany up to a few years ago, although the high risk connected with it had been detected in the 1930's.

The most important medications in these groups are summarized in Tables 6 and 7.

Table 6. HEPATITIS REACTION: I. WITH FREQUENT MASSIVE NECROSIS

Sulfanilamide
Monoamine oxidase inhibitors
Pyrazinamide
Phenyl butazone
6-mercaptopurines
Indomethazine
Halothan
Allopurinol
Frequency: 1/1,000 to 1/10,000
Beginning: 1 - 10 weeks after exposure
Premonitory symptoms: Fever, anorexia
Histology: "Hepatitis" with severe necrosis and cholestasis, mitochondria changed.

Table 7. HEPATITIS REACTION: II. RARELY WITH MASSIVE NECROSIS

PAS
Ethionamide
Diphenylhydantion
Sulfonamides (also long-acting)
α-Methyldopa
Lethality less than in I
Cholestasis clinically and bioptically distinct
Picture similar to possible mononucleosis

This damage is very rare and because of its great similarity / 348 to viral hepatitis is certainly not always recognized as such. In many cases it can also be difficult to distinguish drug-induced damage and virus infection if, for example, the arthralgic preliminary stage of a virus-B-hepatitis is first considered to be polyarthritis and then treated with phenylbutazone. On the

other hand, it is important to observe every medication newly introduced or considered for this reaction. This is important because this reaction has hardly been observed so far in testing with experimental animals. The difficulty is the greater because the jaundice can first appear up to 3 weeks after the medication is stopped.

Halothane hepatitis: Past experience with halothane shows how difficult it can be to blame or to clear a widely introduced medication or anesthetic. Only the costly large halothane study from the United States has brought a certain clarification. Among the 850,000 patients with narcosis, 30% had received halothane. The mortality was 1.87% in the halothane group and 1.93% in the rest of the group. The causes of death included 82 with extensive liver necrosis. Among these were 9 for which no sufficient reason for the liver necroses could be discovered. Of these 9, 7 had received halothane, 4 of them more than once. It appears probable that the disease with severe sequelae occurs only under certain circumstances, with hypersensitivity apparently having a part, and in repeated exposure for some persons. More than half of the fatal cases were cases of repeated cosmetic operations.

The experience teaches that the reaction is manifested by fever 5 - 7 days and jaundice 8 - 11 days after the first exposure. Both fever and jaundice occur after 3 or 5 days on repeated exposure. A two-peaked temperature rise or an elevated temperature lasting for one or more days without other sufficient explanation should warn the critical observer. Leucocytosis and eosinophilia strengthen the suspicion.

From this experience, there is no doubt that halothane can be toxic to the liver in very rare cases. On the other hand, it must be emphasized vigorously that this narcotic which has

proved itself throughout the world, and which anesthetists rightfully regard as an ideal agent, can be used for liver patients. For instance, nearly all patients with liver cirrhosis are narcotized with halothane, without damage, for portocaval anastamosis. The potential chronic liver damage to anesthetists and anesthesia personnel deserves particular attention.

Simultaneously occurring hepatitis-like damage and cholestasis

A series of medications shows in the clinical picture both signs of hepatocellular damage and signs of intrahepatic cholestasis. In most cases the liver damage precedes a general hypersensitivity reaction with skin eruption, fever and blood eosinophilia. Now it appears important to refer to this reaction form in relation with laxative abuse. Only in the last 3 years has oxiphenisatin been recognized as potentially injurious to the liver. Here we are dealing with a medication which has been used for 60 years and is contained in 65 of more than 100 laxative combinations in Germany. Only after this agent had been newly introduced into the American market did we become aware of / 349 the relation. We had already referred, 12 years before, to the probability that laxative abuse can lead to chronic hepatitis or cirrhosis, including the LE cell phenomenon (Klin. Wschr. 38:13-20, 1960). This conjecture was confirmed last year by the observations of Reynolds. Many observations have since been reported. We ourselves have been able to gain the suspicion distinctly on re-exposure of a patient. Seven hours after the re-exposure the patient showed the same changes in the acute stages as 7 years ago.

Direct toxic effect

The direct toxic effect is characterized primarily by a severe liver cell necrosis. The extent of the damage depends on the dose. Correspondingly, one finds clinically all stages

from moderate to extremely high rise in transaminases and, at high doses, a severe acute liver insufficiency with high bilirubin values, hypoglycemia, metabolic acidosis and hemorrhagic diathesis. This syndrome is most familiar to us as carbon tetrachloride poisoning, but carbon tetrachloride cannot be considered among medications. Recently, this type of reaction has become well known, particularly in England, through Paracetamol poisonings. Paracetamol is used as a fever-reducing and analgesic agent. It is sold in Germany as Ben-u-ron (R). It is also a component of many combinations. In England, it appears this agent is often taken with suicidal intent. The lowest fatal dose in man is 15 g. Blood coagulation factors have proved to be the most important prognostic signs. The prothrombin time is extremely reduced and thrombocytopenia and fibrin degradation products indicate severe disturbance of synthetic capacity and intravascular clotting. Lethality from overdose is about 25%.

Severe fatty degeneration of the liver after high tetracycline medication, particularly in pregnancy, is another form of the direct toxic liver damage. The fat consists principally of triglycerides. The tetracyclines prevent exit of the triglycerides from the liver by disturbing synthesis of the lipoproteins necessary for the transport. Like severe acute alcoholic fatty liver, tetracycline fatty liver leads to liver insufficiency which can hardly be differentiated from acute liver dystrophy.

Treatment

The most important measure in the treatment of iatrogenic liver damage is cessation of the suspected agent. In general, drug-induced liver injuries have a favorable prognosis. Otherwise, the same rules apply as for other hepatocellular or cholestatic liver diseases.

Here it is necessary to separate clearly the concepts of toxic damage and drug-induced damage. By far the greatest number of all drug-induced liver injuries are in the group of hypersensitivity reactions. Like all hypersensitivity reactions, the liver damage caused in this way is also a very individual reaction of the host organism. This concept has the result that one should not proceed by a diagram. Thus, it is not allowable to withold from liver patients effective medications which they may require because they have led to liver injuries in a very small number of persons. For instance, there is no need that phenothiazine not be used for patients with cirrhosis /350
of the liver. In my opinion, too, the concept of hepatosis, as it is used in Germany to some extent, is not fortunate. It has been developed in analogy with the concept of nephrosis and we have all witnessed how difficult it was to replace the concept of nephrosis and the concepts linked with it. Originally the suffix "osis" was used as synonomous with "full", as we know in the concept of steatosis, for instance. Full of fat gives a meaning, but full of liver gives no meaning.

We have learned to differentiate certain forms of liver reaction to medications. We separate dose-dependent direct toxic reactions from dose-independent reactions which produce changes which we define as disease units and syndromes, depending on the medication and ability of the organism to react (Table 8).

Table 8. REACTION TYPES IN DRUG-INDUCED LIVER DAMAGE

	Type	Example
Direct toxic action:	1. Necrosis	Paracetamol, Tannic acid
	2. Steatosis	Tetracycline
	3. Cholestasis	Methyltestosterone
Hypersensitivity reaction:	1. Cholestasis	Phenothiazine
	2. Hepatitis	Halothane
	3. Mixed (1 and 2)	PAS, oxyphenisatin
	4. Granuloma	Sulfonylureas

There is some discretion, though, in all the divisions which we have made. But any systematization helps us to bring order into the confusing multiplicity. The person who likes the Berlin idiom can say, with the late roentgenologist Grashey: "Nature hates all systems, but the system is convenient".

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